

Current Status of Hepatic Transplantation

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Since the first human orthotopic liver transplantation on March 1, 1963, 283 patients with various liver diseases had received liver homografts at the University of Colorado and the University of Pittsburgh by February 28, 1983. During this 20-year period many scientific observations and surgical technical improvements were reported from the experience in liver transplantation.¹⁸ However, significant improvement of survival after liver transplantation had to await the discovery and clinical use of cyclosporine, a potent immunosuppressive agent derived from the fungi *Cyclidocarpon lucidum* and *Trichoderma polysporum*.^{1,2,5,7,21,26}

We report here the current status of hepatic transplantation, mainly focusing on the 100 consecutive liver recipients who were treated with cyclosporine and low-dose prednisone since March, 1980.

RECIPIENT SELECTION

Age

Although a 7-month-old baby with neonatal hepatitis and a 57-year-old man with hepatoma in a cirrhotic liver are alive 16 months and 12 months, respectively, after liver transplantation, it is desirable that the recipient be between 1 year and 50 years of age. Surgical technical complications are more common in very small infants, and cardiopulmonary complications are frequent in elderly recipients.

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Infections

Infection is the most common cause of death after liver transplantation.^{6,13,14,21,24,25} Significant pulmonary, urinary tract, and biliary tract infections must have been eradicated before transplantation. Spontaneous peritonitis is common in cirrhotic patients.

Virus infection is aggravated by immunosuppression therapy. Hepatitis B virus, documented by HBsAg or e-antigen, persists or reappears after a short period and leads to chronic aggressive hepatitis of the graft.^{8,21} Nevertheless, we are still accepting candidates with positive HBsAg, but are attempting to modulate the course of viral hepatitis by hyperimmune globulin, vaccination, and/or interferon therapy.

Malignancy

Malignant tumors grow more aggressively under immunosuppression therapy.¹⁸ Malignancy outside the liver must be proved to be cured before consideration of transplantation. Primary malignancy of the liver is one of the indications for liver transplantation, but the incidence of recurrence has been very high if the recipients live long enough.^{3,6,10,21,24,25} Metastatic tumor to the liver is not an indication for liver transplantation.

Other Conditions

Severe mental retardation, uncontrolled psychiatric disorders, alcoholism, and drug abuse before rehabilitation create unsuitable conditions for transplantation. Uncomplicated diabetes mellitus is a relative contraindication for liver transplantation. Diabetes has been treated by simultaneous pancreas transplantation.⁴ Disabling cardiopulmonary diseases are contraindications for liver transplant, unless heart and/or lung transplantation is con-

sidered at the same time. However, such a drastic procedure has never been done. Renal failure from hepatorenal syndrome is not a contraindication.¹¹ Active gastrointestinal bleeding should be controlled before transplantation. Deep hepatic coma (grade 4) with severe brain edema may progress to herniation and brain death before the graft liver reverses the pathology.

Timing

Many of the early deaths after transplantation have been attributable to the poor condition of the recipients. The assessment of timing of transplant for acute liver failure is much more difficult than that of chronic liver failure. Moribund patients cannot be saved by liver transplantation. Transplantation too late in the course of either chronic or acute disease is as unjustified as transplantation too early. If the patient is chronically hospitalized or house-bound, or the patient cannot conduct a reasonably satisfying life because of liver disease, liver transplantation may be offered.

RECIPIENT WORK-UP

By the time candidates are brought into the transplant center for final evaluation, they are often too ill to undergo extensive investigation of their illnesses. Mild sedation for endoscopy has led to hepatic encephalopathy and/or aspiration pneumonia, and prolonged starvation for tests or contrast media for radiologic tests has introduced frank renal failure to the candidates who have marginal hepatic and renal function. Most of the candidates with chronic liver disease have already had extensive work-up for their disease. Careful review of past medical records is often all that is necessary.

A guideline of recipient work-up is shown in Table 1. If the etiology of the liver disease has been established, it is excessive to check all the tests listed in Table 1.

Noninvasive radiographic procedures, such as ultrasonography and computed tomography, are quite useful in assessing the anatomy of and surrounding the liver, and they decrease the need of invasive angiography. Patency and size of the portal vein and the inferior vena cava can be determined quite accurately by ultrasonography. If these are not identified by ultrasonography and/or computed tomography (CT), angiography is indicated. The size of the liver and the extent of any tumor can be accurately determined by CT and ultrasonography. If the biliary ducts are shown to be dilated by ultrasonography and/or CT, endoscopic retrograde cholangiography or transhepatic needle cholangiography may be indicated.

TABLE 1. A Guideline of Recipient Work-Up*

1. Complete history and physical examination.
Review of past medical records.
Body weight, height, and abdominal girth.
Vital signs, intake and output, nutritional evaluation.
2. Urinalysis and occult stool blood.
3. Complete blood count, platelet count, serum sodium, potassium, chloride, carbon dioxide, calcium, phosphorus, magnesium, blood urea nitrogen, creatinine, total protein/albumin, total bilirubin/direct, SGOT, SGPT, alkaline phosphatase, gamma glutamyl transpeptidase, lactate dehydrogenase, amylase, glucose and ammonia, prothrombin time and partial thromboplastin time, blood gas.
4. Cultures (such as blood, urine, sputum, ascites).
5. Blood typing and antibody screen.
Hepatitis A and B screen.
Coagulation profile.
HLA-A, B, and DR typing and cytotoxic antibody screen.
6. Ceruloplasmin, alpha-1-antitrypsin level and phenotype, anti-mitochondrial antibody, antinuclear antibody, antismooth muscle antibody, serum iron, ferritin. Lupus erythematosus preparation. Serum protein electrophoresis, quantitative immunoglobulins.
7. Antiviral antibody titers.
8. Chest x-ray. Ultrasonography, computed tomography (CT) scan, cholangiography, angiography, upper and lower gastrointestinal series.
9. Endoscopy (panendoscopy, endoscopic retrograde cholangiopancreatography, colonoscopy).
10. Ophthalmologic examination.
11. Neuropsychiatric evaluation, brain CT scan, electroencephalogram.
12. Social worker evaluation.
13. Freeze serum and plasma for future investigation.

*Limit the tests to absolute minimum for proper diagnosis and treatment.

Cultures of all sources are indicated even in the absence of fever, leukocytosis, or any clinical sign of infection.

DONOR-RECIPIENT MATCHING

Liver Size

Matching the size of donor and recipient is quite important in order to avoid technical difficulties in surgery. With the shrunken livers of cirrhosis, a smaller donor than recipient is usually desirable.

ABO Blood Group

In organ transplantation group O patients can be considered universal donors and group AB patients are universal recipients.¹⁷ Although the liver graft is resistant to hyperacute rejection and ABO blood group incompatible grafts have functioned for years,^{21,24,25} this practice should be limited to absolutely life-threatening situations.

T-Warm Cross-Match

Liver transplantation has been performed against the recipient antidonor T-warm antibodies, which cause hyperacute rejection of kidney homografts.^{9,21,24,25} There has been no hyperacute rejection of liver homografts to our knowledge. Graft survival of positive T-warm cross-match donors has been about the same as that of negative cross-match donors. A positive T-warm cross-match is not a contraindication to liver grafting.

HLA Typing

The time constraints of liver preservation and the urgent recipient need preclude efforts at tissue matching at the A, B, and DR (D-related) histocompatibility loci.

DONOR OPERATION

The satisfactory early function of transplanted whole organs is largely dependent upon procurement techniques that minimize ischemic injury. The amount of ischemia, warm or cold, that an organ can tolerate and still provide life-sustaining function following transplantation is different for each organ system. When compared with livers and hearts, kidneys are relatively more tolerant of both warm and cold ischemia. Using the techniques to be outlined, the incidence of first week dialysis in patients receiving renal allografts procured in combination with livers or hearts or both is less than 10%.^{15,16} In addition satisfactory livers or hearts usually can be obtained unless there has been faulty donor selection.

Technique

A long midline abdominal incision combined with a midline sternotomy provides excellent exposure.^{15,16} After gross inspection of the organ to determine suitability, the initial dissection is done by the liver team. Anomalies of hepatic arterial supply are identified and preserved. The celiac axis (and superior mesenteric artery if it has a hepatic branch) is dissected back to the origin from the aorta, and all nonhepatic branches are ligated and divided. The hilar dissection is completed by dividing the common bile duct as close to the duodenum as possible, followed by isolation of the portal vein. The pancreas can be divided between mass ligatures to gain better exposure of the splenic and superior mesenteric veins. Attention is then turned to a complete division of all of the supporting ligaments of the liver. The suprahepatic vena cava is encircled.

This maneuver is facilitated by individual ligation of the phrenic veins.

Once the hepatic dissection is completed, the nephrectomy team proceeds to mobilize both kidneys and ureters.

The next step involves cannulation of the distal aorta and vena cava at the iliac vessels and placement of a catheter into the splenic vein.

The most critical step at this point for proper preservation of the liver is to begin a precooling stage by infusion of cold (4°C) lactated Ringer's solution into the portal venous system via the splenic vein cannula. The superior mesenteric vein and artery are ligated simultaneously beginning with this infusion. Because arterial circulation is intact, this provides nonischemic core cooling to the large mass of hepatic tissue. It has the added advantage of cooling the entire cadaver, thus further protecting the other organs. If the heart is to be procured, the cardiac team can complete its dissection at this time.

The proper sequencing of organ removal requires cooperation among the various teams. Hepatic precooling is complete when several liters have been infused and donor temperature has reached 28 to 30°C. If the heart is to be taken, it is removed first. The abdominal aorta is clamped at the diaphragm and the cannula in the distal aorta opened as soon as circulatory arrest is effected by the cardiectomist. Simultaneously, the vena cava cannula is opened and allowed to drain freely. The portal vein infusion is changed from an extracellular (lactated Ringer's) to an intracellular (modified Collins solution) composition for a final flush of 500 to 1500 ml. The composition of the aortic flush solution is the choice of the nephrectomy team, but most often is Collins solution or one of its modifications. The advantage of this *in situ* flush of the kidneys is the complete elimination of warm ischemia.

Once removed, the organs are placed in an ice bath and inspected. They are stored and transported in ice slush, although kidneys may also be preserved with pulsatile pump perfusion.

At the present time, hepatic allografts for clinical use are transplanted as soon as possible following removal. Cold ischemia up to 12 hours has been tolerated, but an effort is made to keep this time under 5 or 6 hours.

RECIPIENT OPERATION

The principles of recipient hepatectomy and orthotopic liver transplantation were established 15 years ago¹⁸ and have not been changed, with the exception of minor modifications.^{21,24,25} Originally,

splenectomy was performed at the time of transplantation if it had not been carried out at an earlier time. One of the reasons was that with the hypersplenism and leukopenia of portal hypertension an adequate amount of azathioprine could not be administered because of its known bone marrow suppressive activity. At present, splenectomy is almost never necessary. Cyclosporine usually does not depress bone marrow function, and hypersplenism, if it exists prior to liver transplantation, will improve or disappear after a successful liver transplantation.

Recipient hepatectomy is usually performed by dissecting the hilar structures and the vena cava above and below the liver, and by then cross-clamping and dividing the various vessels just as the liver is removed.^{18,25} However, in some cases, a safer way has been to transect the hilar structures first and the infrahepatic vena cava when all else is in readiness. Then, by pulling on clamps that are placed on the hepatic side of these structures, the liver is dissected free from below to above, ligating all tissues on the way. The vena cava above the liver remains intact as the stalk of the specimen until it is clamped just before the liver is removed.²⁵

During the implantation of the new liver, it is necessary to occlude the splanchnic and vena caval

circulations. Most patients can survive this insult. In recent cases, venovenous bypass of these venous beds without heparinization has been used. This venovenous bypass system without heparin has provided promising preliminary results.

Completed orthotopic liver transplantation is shown in Figure 1. The usual order of anastomoses is as follows: (1) suprahepatic vena cava; (2) infrahepatic vena cava followed by a washout of high potassium preservation fluid with Ringer's lactate solution through the portal vein; (3) portal vein, after which the liver is partially vascularized; (4) hepatic artery, and (5) biliary system.

End-to-end choledochocholedochostomy with T-tube or straight tube stent has been our choice when both donor and recipient bile ducts are suitable for anastomoses (Fig. 1-A). If the recipient bile duct is diseased or absent end-to-side choledochojejunostomy in Roux-en-Y is chosen (Fig. 1-B). The gallbladder is not used for biliary reconstruction except for unusual circumstances.^{21,24,25}

IMMUNOSUPPRESSION WITH CYCLOSPORINE

Cyclosporine is administered before liver grafting in an oral dose of 17.5 mg/kg or an intra-

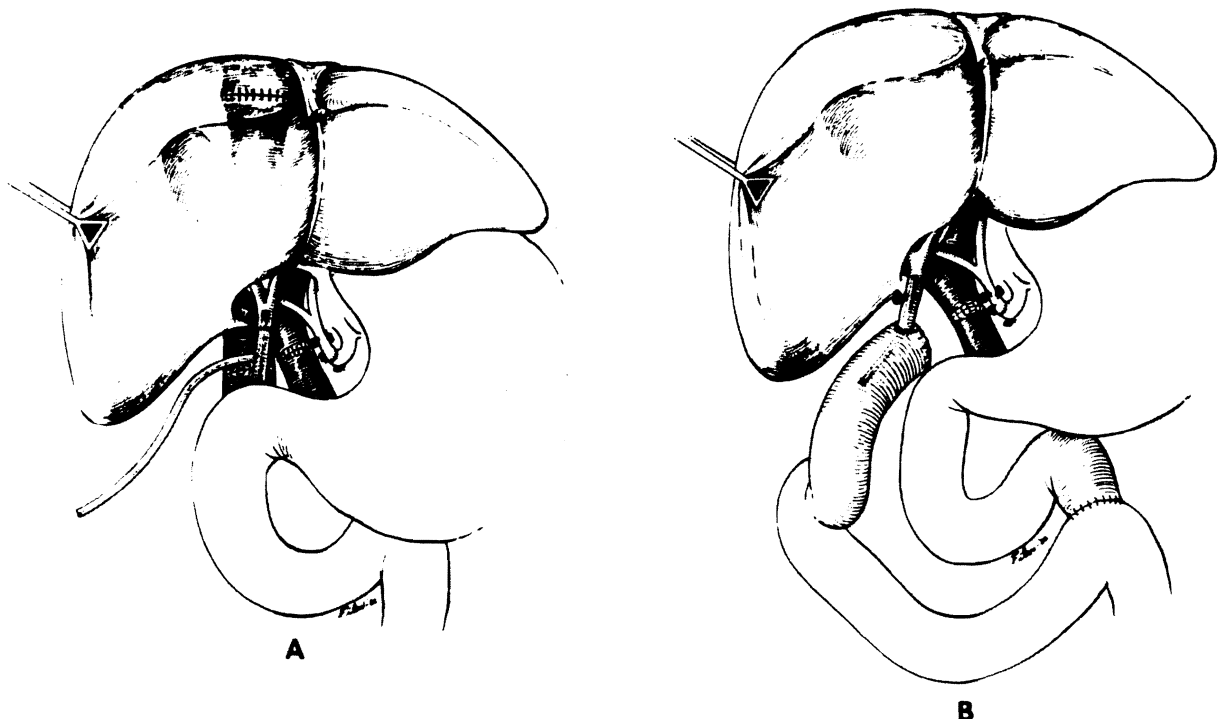


FIG. 1. Completed orthotopic liver transplantation. A: Biliary tract reconstruction with choledochocholedochostomy. B: Biliary tract reconstruction with choledochojejunostomy in Roux-en-Y. (Reproduced with permission from Starzl et al.²¹)

venous dose of 5 mg/kg. Soon after the operation, cyclosporine is given intravenously as a dose of 2 mg/kg every 8 hours. When the patient can resume oral intake, 17.5 mg/kg of cyclosporine in two divided doses is given in addition to the intravenous doses. Intravenous cyclosporine is gradually withdrawn, depending upon the renal function, the blood level of cyclosporine, and graft function. Maintenance dosage of cyclosporine is adjusted, mainly based on the nephrotoxicity of the drug,¹² and usually it is in the 10 mg/kg/day range at 1 month and 8 mg/kg at 6 months. Children seem to tolerate the drug better than adults, and their maintenance dose of cyclosporine is higher than that of adults.

Steroids are necessary in addition to cyclosporine to achieve adequate immunosuppression, but the dose is much less than that required in combination with azathioprine.^{19-23,26} One gram of methylprednisolone is administered intravenously soon after revascularization of the liver graft. Postoperatively, methylprednisolone or prednisone is given to adults in dosages of 200 mg/day on the first day, and the dose is decreased by 40 mg daily until the daily maintenance dose of 20 mg is reached on the sixth day. Further reduction of the steroid dose depends upon graft function. Usually the patient is discharged with a daily maintenance dose of prednisone of less than 15 mg 1 to 2 months after transplantation. Initial and maintenance doses of steroids are reduced in infants and children.

If rejection occurs in spite of the immunosuppressive therapy outlined, boluses of intravenous steroid therapy (1 gm of hydrocortisone or methylprednisolone) and/or a recycle of the original 5-day burst of prednisone therapy are given immediately. Although cyclosporine does not permit much dose maneuverability, it is sometimes possible to increase the dose in spite of the risk of nephrotoxicity.

INDICATIONS FOR LIVER TRANSPLANTATION

Indications for liver transplantation in 40 pediatric patients and in 60 adults are listed in Tables 2 and 3. The indications for one-half of the pediatric liver transplantations were biliary atresia or hypoplasia. All of the children with biliary atresia had had porticoenterostomy (Kasai operation). The three most common indications for adults were chronic aggressive hepatitis with cirrhosis, primary biliary cirrhosis, and primary liver malignancy.

Three of the 21 patients (3 children and 18 adults) with chronic aggressive hepatitis were positive for hepatitis B surface antigen (HBsAg). All three patients were treated with hepatitis B hyper-

TABLE 2. Indications for Transplantation in Pediatric Patients (≤ 18 Years) Among 100 Consecutive Patients Treated with Cyclosporine-Steroid Therapy

<i>Liver Pathology</i>	<i>No.</i>
Biliary atresia*	20
Alpha-1-antitrypsin deficiency†	6
Chronic aggressive hepatitis	3
Byler's disease‡	3
Secondary biliary cirrhosis§	1
Budd-Chiari syndrome	1
Neonatal hepatitis	1
Subacute Wilson's disease†	1
Tyrosinemia‡	1
Type I glycogen storage disease†	1
Sea-blue histiocyte syndrome†	1
Cellular inflammatory pseudotumor	1
Total	40

*Two had Alagille's syndrome.

†Inborn errors of metabolism. The children with tyrosinemia and sea-blue histiocyte syndrome had incidental hepatomas in their cirrhotic livers.

‡Diagnosis equivocal in one case.

§Choledochal cyst with multiple operations.

TABLE 3. Indications for Transplantation in Adult Patients (≥ 19 Years) Among 100 Consecutive Patients Treated with Cyclosporine-Steroid Therapy

<i>Liver Pathology</i>	<i>No.</i>
Chronic aggressive hepatitis	18
Primary biliary cirrhosis	12
Primary liver malignancy*	11
Sclerosing cholangitis	7
Secondary biliary cirrhosis†	4
Budd-Chiari syndrome	3
Alpha-1-antitrypsin deficiency	2
Alcoholic cirrhosis	2
Adenomatosis*	1
Total	60

*One patient in each group had previous (1 and 4½ years earlier) right hepatic trisegmentectomy. At transplantation, the regenerated left lateral segment was replaced with a whole liver.

†Including two trauma and one each of Caroli's disease and choledochal cyst.

immune globulin immediately after liver transplantation. Despite this, all three patients, after brief periods of negative HBsAg, became HBsAg positive and developed chronic active hepatitis.²¹ None of the 12 patients with primary biliary cirrhosis have developed clinical and histologic evidence of recurrence in spite of the reappearance of antimitochondrial antibodies in two patients.²¹

Thirteen patients with primary liver malignancy (2 children with incidental hepatoma and 11 adults) received liver transplantation. Three adults died from recurrent tumor after 9 months (Klatskin tumor), 12 months (cholangiocarcinoma), and 32 months (fibrolamellar hepatocellular carcinoma). Seven of the 13 patients are alive free of tumor 6 to 21 months after transplantation. Our previous ex-

perience^{10,21,24,25} indicates that malignant tumor will recur in most cases, if the malignancy is known before transplantation, but that if the malignancy is an incidental finding of pathologic examination or the malignancy is absolutely confined to the liver, cure can be achieved by total hepatectomy and liver replacement (orthotopic liver transplantation). Selection of the patients with primary liver malignancy is extremely difficult.

CAUSES OF DEATH

It is often difficult to categorize the cause of death after liver transplantation, because most of the deaths are due to multiple organ failure. However, the causes of death within a year after liver transplantation among 100 consecutive patients with cyclosporine-steroid therapy were classified to the best of our knowledge as shown in Table 4.

Seven patients died during or soon after the operation. Three of the seven had abnormally small portal veins and attempts to obtain adequate portal flow from the confluence of the splenic and superior mesenteric veins resulted in fatal hemorrhage. Two patients had had portacaval anastomoses and satisfactory portal vein anastomoses could not be achieved. One patient had had multiple surgeries for a shotgun wound of the liver, and a combination of biliary fistula, abscess, and dense scar tissue made the operation unsuccessful. One child with biliary atresia had hypotension and cardiac arrest during the cross-clamping of the suprahepatic and infrahepatic vena cava. Anastomoses were completed, but the patient was brain dead at the end of the operation. Postmortem examination revealed the absence of superior vena cava and collateral veins from the upper body draining into the inferior vena cava below the renal veins. This patient died from brain congestion during the cross-clamping of the inferior vena cava.

Eight patients died from various surgical technical complications several days to 3 months after liver transplantation. Two children died from

hepatic artery thrombosis, and two others died from both hepatic artery and portal vein thrombosis. All four of these children had abnormal hepatic arteries and/or hypoplastic portal veins and two of them had venous homografts, one for the hepatic artery and another for the portal vein, to establish satisfactory inflow to the liver graft.

One child had had portal vein thrombosis after a previous splenectomy, and the graft portal vein inflow was substituted by portacaval transposition. However, the portal vein was thrombosed several days later and the child died from liver failure. Another child with biliary atresia did not have an inferior vena cava and the hepatic vein, which was anastomosed to the right atrium, was twisted and thrombosed after transplantation. A third child developed a leak from choledochojejunostomy and an abscess formed at the hepatic hilum. An attempt to drain the abscess and to reconstruct the biliary system led to fatal hemorrhage from the portal vein.

Surgical technical complications have been less common in adults than in children. One adult patient developed hematemesis due to mycotic aneurysm of the hepatic artery. The hepatic artery was replaced with a homograft, but ruptured a week later due to infection. This patient died suddenly from exsanguination.

Five patients died after being given unsatisfactory liver grafts that had been damaged before or at the time of organ harvest. Four of the five poor grafts were the first four liver transplantations in Pittsburgh. Since then, procedures of multiple organ procurement in cooperation with other transplant teams have been standardized as described previously.

Ten patients died from liver failure due to acute and chronic rejection. However, most of these patients developed serious infectious complications during the aggressive treatment for rejection with high doses of steroids.

Seven patients died from infectious complications in the abdomen (3), lungs (3), and throat (leading to asphyxiation, 1).

Two patients died with liver failure due to recurrent or persistent chronic aggressive (HBsAg positive) hepatitis after liver transplantation. One of them also developed pulmonary sepsis and another necrotizing pancreatitis at the end of their lives.

One patient died from recurrent Klatskin tumor 9 months after liver transplantation. Another patient with alpha-1-antitrypsin deficiency disease died from graft failure due to persistent hypoxia caused by pulmonary arteriovenous shunts, which did not close despite a successful liver transplantation.

For further improvement in survival, it is worthwhile to note that at least ten early deaths could have been avoided if the patients with abnor-

TABLE 4. Main Causes of Deaths Within a Year Among 100 Consecutive Liver Recipients Treated with Cyclosporine-Steroid Therapy

<i>Major Causes</i>	<i>No.</i>
Intra- and perioperative death	7
Surgical technical complications	8
Unsatisfactory liver graft	5
Graft rejection	10
Infection	7
Recurrent hepatitis B	2
Recurrent malignancy	1
Other*	1

*Graft hypoxia due to marked pulmonary arteriovenous shunt.

malities of the portal vein, hepatic artery, or vena cava had not been accepted as liver transplant candidates. However, this kind of surgical technical challenge may be justified, because a similar number of patients with these anatomic disadvantages have been saved by liver transplantation.

IMPROVED SURVIVAL

The actuarial survival calculated from the 67 consecutive cases treated with cyclosporine-steroid therapy since 1980 were compared with the actual survival of 170 consecutive cases treated with azathioprine-steroid and/or antilymphocyte globulin between 1963 and 1979 (Fig. 2). The survival after liver transplantation obtained at Cambridge-King's College, England, was calculated from their published reports^{3,6,7} and is also shown in Figure 2 for comparison.

Since the introduction of cyclosporine-steroid therapy to our standard immunosuppression regimen, the survival after liver transplantation has doubled. Although long-term survival with cyclosporine-steroid therapy is limited to 3 years, current data suggest that a 5-year survival of 50% will be achieved in the near future.

CONCLUSIONS

The number of human orthotopic liver transplantations is rapidly approaching 500, of which approximately 90% have been performed by two groups: Starzl and associates at Denver and Pittsburgh, and Calne et al at Cambridge. The combina-

tion of a successful surgical technique and the improved immunosuppression offered by cyclosporine give every promise of providing a 50% 5-year survival in appropriately selected patients. These experiences indicate that the time has come for the creation of additional centers capable of performing this procedure.

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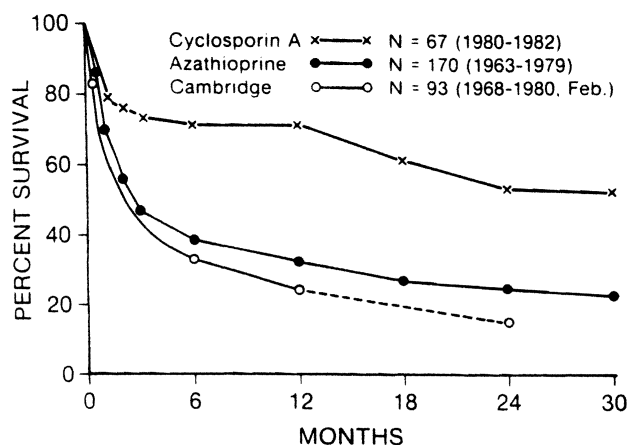


FIG. 2. The actuarial survival of patients with cyclosporine and low-dose steroids compared with that obtained with conventional azathioprine, steroids, and antilymphocyte globulin by the authors and that by the workers at Cambridge. The data for the Cambridge curve were obtained from published reports. (Reprinted with permission from Calne et al.^{3,7})

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